REMARKS

I. STATUS OF THE CLAIMS

After amendment, claims 1-26 and 28-39 are pending. Applicants amended claims 17, 18, 31, and 34-36 to correct typographical errors. Applicants canceled claim 27 and amended claim 26 to incorporate the limitations of claim 27. Applicants added new claims 37-39. Support for these amendments can be found at least in the specification and claims as originally filed. Support for new claims 37-39 can at least be found in the specification at page 21 lines 16-26 and Table 8 on page 82. Accordingly, no new matter has been added by these amendments to the claims.

II. EXAMINER INTERVIEW

Applicants thank the Examiner and Supervisor for granting an in person interview on April 15, 2008. The 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 103 rejections were discussed and the Office stated that a declaration consistent with Applicants' arguments at the interview would place the application in condition for allowance. The substance of the interview is captured by this response.

III. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejected claims 6 and 24-28 under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action at page 2. Specifically, the Examiner asserts that there is insufficient antecedent basis for the limitation "the at least one other physiologically acceptable gas" in lines 1-2 of claims 6, 24 and 25 and the limitation "the other physiologically acceptable gas" in lines 2-3 and 7 of claim 26, and lines 3-4 of claim 27.

Applicants respectfully submit that the current language is clear and, as discussed in the interview, the Office agreed that the rejection would be withdrawn.

IV. REJECTION UNDER 35 U.S.C. § 103

The Examiner rejected claims 1-36 under 35 U.S.C. § 103 over *Osman* et al. WO 00/72821 (International Application Published Under the PCT, Published 12/07/2000). Specifically, the Examiner asserted that *Osman* teaches "a gas phase comprising carbon dioxide, oxygen, and minor amount of nitrogen gas." Office Action at page 4. The Examiner conceded that *Osman* does not teach the specific amounts of nitrogen gas claimed, 0.0001 to 0.8%, but asserted that the claimed range of nitrogen gas is obvious because *Osman* "teaches a gas phase comprising preferably 70 to 80% oxygen, 20 to 30% carbon dioxide, and a minor amount of nitrogen," therefore the composition may comprise between 0 to 10% nitrogen "which covers the instantly claimed concentration of 0.01 to 0.6% nitrogen." *Id.* at pages 4-5. Applicants respectfully traverse.

As agreed at the interview, Applicants herein submit a declaration by Dr. Janet Rush in support of their arguments

It is the Examiner's position that a *prima facie* case of obviousness exists when the claimed ranges overlap or lie inside ranges disclosed in the prior art. M.P.E.P. § 2144.05. However, "a patentable invention may lie in the discovery of the source of a problem though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. 103." *In re Sponnoble,* 405 F.2d 578, 585, 160 U.S.P.Q. 237 (C.C.P.A. 1968). Moreover, even

assuming a *prima facie* case of obviousness, "Applicants can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range." *Id.* Criticality is generally shown by demonstrating that "the claimed range achieves unexpected results relative to the prior art range." *Id.* (citing *In re Woodruff,* 919 F.2d 1575, 16 U.S.P.Q.2d 1934 (Fed. Cir. 1990). A *prima facie* case of obviousness may also be rebutted by showing that the prior art, in any material respect, taught away from the claimed invention. *Id.*

As discussed at the interview, Applicants assert that even assuming that the claimed invention is *prima facie* obvious in view of *Osman*, the evidence provided herein demonstrates the patentability of the claimed invention. Specifically, as explained herein: (1) the prior art, in a material respect, taught away from the claimed invention, (2) prior to Applicants invention there was no recognition or discovery of the potential for side effects from foams made with low levels of nitrogen (e.g., 7%), and (3) it is unexpected that the instant foam achieves a result not seen using a foam with low levels of nitrogen (e.g., 7%). As agreed at the interview, Applicants submit the enclosed declaration of Dr. Janet Rush in support of these arguments. *See Rush* declaration and supporting documents, attachment A and Appendix 1,2 and 3.

The prior art teaches away from the claimed invention

Since the late 1990's, foams made with a liquid sclerosant and air have been widely used to treat varicose veins in the U.S. and Europe. *See Rush* declaration, attachment A at ¶5. There was no motivation to remove essentially all nitrogen from sclerosing foams, as claimed herein, because the prevailing thought at the time was that lowering the amount of foam (and therefore lowering the volume of polidocanol and

nitrogen) was sufficient to ensure the safety of the procedure. Nothing in the prior art suggested that by minimizing the percentage of nitrogen to the extremely low levels currently claimed, the size of any enduring bubbles could be reduced to a level where their physiological impact can be eliminated or at least rendered insignificant.

For example, prior to Applicants' invention, it was well known in the art that the use of air foams containing sclerosing agents such as polidocanol caused undesirable, and sometimes serious, side effects. These include migraines, tissue necrosis, sight problems, vomiting, and thrombosis. *See e.g., Benigni*, attachment B; *Bergan*, attachment C; *Henriet*, attachment D. More serious side effects such as stroke have also been seen. *See e.g., Forlee*, attachment E.

The prevailing thought at the time, and even by many today, targets polidocanol as the main cause of these side effects and, therefore, practitioners were simply lowering the amount of foam used in order to effectively lower the concentration of polidocanol. *See e.g., Henriet*, attachment D, *see also Lang* declaration, attachment F. As one commentary stated:

> Colleagues with a surgical background are used to treating varices patients in a single therapy session when possible. We know that this aim is often unrealistic with sclerotherapy and can only be achieved at the cost of a marked increase in the rate of adverse effects. **For this reason there is an international tendency to use smaller quantities of foam as we recommended at our European Consensus Conference back in 2003.**

Breu, attachment G (emphasis added). Thus, even in view of the fact that less foam requires numerous, repeat treatments, the art teaches lower doses of foam as the preferred way to reduce the potential for side effects. *See e.g.,* U.S. Patent Application

Publication No. US 2008/0050436 A1, attachment H at ¶ 0011 ("Due to the concerns of using too much sclerosant at one treatment, sclerotherapy generally requires multiple treatment sessions at intervals.").

Similarly, it was also widely thought that high volumes of certain gases, particularly nitrogen, which is only slightly soluble in blood, was contributing to side effects by producing stable bubbles that could travel to other sites, including the brain. *See* U.S. Patent Application Publication No. US 2008/0050436 A1, attachment H, at ¶ 0016 ("However, gas (air, CO_2, etc.) is used to form the foams, and there is concern about the solubility of the gas in the body. The undissolved foams may flow to artery and other organs and cause gas embolism. If the patient has a patent foramen ovale [a hole in the heart], the foams can travel to the brain and may cause serious side effects such as stroke."). Notwithstanding these concerns, air (comprising 80% nitrogen gas) continues to be widely used based on the belief in the art that a lower volume is sufficient to ensure safety. *See e.g., Frullini,* attachment I ("The safe amount of injected air is, at the moment, 3 ml per session.").

Therefore, the prevalent solution to the problem of side effects was to use a lower volume of foam in order to effectively lower the volume (but not concentration) of nitrogen gas and sclerosing agent. Practitioners choose to use a lower volume of foam even though it is less efficacious and requires multiple treatments to effectively sclerose the vein. As such, the prior art teaches away from the claimed invention and the use of very low percentages (<0.8%) of nitrogen gas in that (1) the art teaches that large volumes of foam, regardless of gas content, can be harmful, (2) air is still used

predominantly in foam sclerotherapy, and (3) the art, at best, teaches lowering the volume of nitrogen gas to avoid potential side effects.

Applicants were first to recognize that even residual amounts of nitrogen in a foam could cause side effects

In a study commissioned by Applicants, Eckman et al. demonstrated that a sclerosant foam made with air (i.e. 80% nitrogen gas) could block the circulation of blood in rat cremaster vessels. *See Eckman*, attachment L; *Rush* declaration, attachment A at ¶6.

Surprisingly, however, Applicants found, in their clinical work, that replacing air foam with foams only containing 7% nitrogen still resulted in some incidents of transient neurological and visual effects. *See Rush* declaration, attachment A at ¶7. Specifically, Applicants observed that a foam containing only 7% nitrogen caused transient neurological and visual effects in 1.4% of patients compared with 0.8% of the patients treated with foam made with room air. *Id.*

Practitioners, including *Osman,* did not recognize that side effects could be caused even by residual small volumes of nitrogen gas. For example, *Osman* focuses on removing large volumes of nitrogen (less than 50%). *Osman*, noting that nitrogen gas is almost twice as insoluble in water as oxygen, states that "[f]urthermore, a problem in using air as the gas for producing the foam is the perception that large volumes of nitrogen should not be unnecessarily introduced into patients, particularly where large vessels are being filled with foam and eliminated. Gas embolism with nitrogen remains a possibility." *Osman* at page 3, lines 6-9 (emphasis added). Therefore, "[t]he other [than CO_2] components of this gas are preferably oxygen with a

minor proportion only of nitrogen being preferred." *Osman* at page 9, lines 9-10 (emphasis added). In summary, *Osman* discloses the use of a broad range of nitrogen gas concentrations and teaches that some nitrogen gas is preferred. *Id.*

Applicants recognized, however, that simply reducing the amount of foam, and thereby the volume of nitrogen, will not necessarily solve the problem of harmful side effects. *See Rush* declaration, attachment A at ¶¶6-7. Surprisingly, Applicants found that regardless of the volume of foam, the size of bubbles will still be the same since the residual bubble size is dictated by the percentage of nitrogen in the gas mixture.

Indeed, the FDA agreed with Applicants discovery. A clinical hold was instituted on approval of foam sclerosants after determining that microbubbles in foam containing nitrogen gas were traveling to the brain. *See* FDA presentation, attachment J. The FDA found evidence of micro-infarcts, *e.g.,* neurological problems and visual disturbances, and detected microbubbles in the middle cerebral artery (MCA) in some patients. *Id.*

It is unexpected that the instant foam achieves results not seen using foams of the prior art

To date, results in both *in vivo* and clinical testing have been achieved with the claimed foam that were not seen with foams of the prior art.

Surprisingly, the low amounts of nitrogen of the claimed invention demonstrated a visible difference in the number of bubbles circulating in rat cremaster vessels not seen with prior art foams. For example, the Eckman study demonstrated that when a foam containing 7% nitrogen was injected into rats, visible bubbles were seen in the cremaster vessels of 5 out of 6 animals. In contrast, bubbles were observed in only 1

out of 6 animals treated with foam containing less than 0.8% nitrogen. *See Rush* declaration, attachment A at ¶8.

Additionally, as Dr. Rush explains in her declaration, the benefits of the claimed foam are also currently being seen in human clinical trials. In a phase II safety study of the claimed foam the incidence of MRI lesions, neurological or other visual field abnormalities, and elevated cardiac markers has been reduced, if not eliminated. *See* BTG press release, attachment K; *Rush* declaration, attachment A. The study investigator stated that "[i]t is clear that patients undergoing microfoam endovenous occlusion are commonly exposed to gas bubbles in the cerebral arterial circulation. Exposure to this proprietary microfoam, which has a controlled density, bubble size and gas mix, has not been associated with evidence of microinfarction." BTG press release, attachment K.

Specifically, of the 87 patients administered the claimed foam (new Varisolve® foam, less than 0.8% nitrogen), 42 of which had bubbles detected in the middle cerebral artery[1], none displayed visual disturbances or neurological symptoms within the first 24 hours after treatment. *See Rush* declaration, attachment A at ¶13. In contrast, 1.7% of patients treated with the old (7% nitrogen) Varisolve® foam displayed visual disturbances or neurological symptoms within the first 24 hours after treatment. *See Rush* declaration, attachment A at ¶14.

Therefore, Applicants have demonstrated that (1) the prior art, in a material respect, taught away form the claimed invention, (2) there was no recognition of the

[1] Bubbles detected in the middle cerebral artery suggests a right to left cardiac shunt, which is thought to allow bubbles to enter the brain.

potential for side effects with foams of low amounts, *e.g.,* 7%, of nitrogen gas, and (3) it is unexpected that the instant foam achieves a result not seen using a foam with low levels of nitrogen, and have therefore rebutted any *prima facie* case of obviousness. For at least the above reasons, Applicants respectfully request withdrawal of the rejection as to claims 1-36 under 35 USC § 103.

V. CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of claims 1-36 and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: May 1, 2008

By: _____
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Attachments:

A. *Rush, J.,* declaration, April 29, 2008, and supporting documents, *Rush and Wright*, Letter to the Editor, *N. Engl. J. of Med.,* Appendix 1; *Ceulen et al.,* Microembolism during foam sclerotherapy of varicose veins, *N. Engl. J. Med.* (2008) 358:1525-26, Appendix 2; and *Regan et al.,* Safety of proprietary sclerosant microfoam for saphenous incompetence in patients with R-to-L shunt: Interim Report., *J. Vasc. Interv. Radiol.* (2008) 19:S35 (meeting abstract), Appendix 3.

B. *Benigni, J.P.,* Foam Sclerotherapy and Migrane with Aura, *Phlebologie,* English translation (2005).

C. *Bergan et al.,* Extensive Tissue Necrosis Following High-Concentration Sclerotherapy for Varicose Veins, *Dermatol. Surg.,* (2000) 26:535-542.

D. *Henriet, J.P.,* Three year experiment using polidocanol foam in the treatment of reticular varices and varicose veins, *Phlebologie,* English translation.

E. *Forlee et al.,* Stroke after varicose vein foam injection sclerotherapy, *J. Vasc. Surg.* (2006) 43:162-4.

F. *Lang, W.,* declaration, October 23, 2007.

G. *Breu, F.X.,* Reversible neurological complications from foam sclerotherapy, Commentary on Forlee MV et al., *Phlebologie,* English translation (2006).

H. *Chu, J.F.,* U.S. Patent Application Publication No. US 2008/0050436 A1.

I. *Frullini et al.,* Sclerosing Foam in the Treatment of Varicose Veins and Telangiectases: History and Analysis of Safety and Complications, *Dermatol. Surg.* (2002) 28:11-15.

J. *Khin Maung U,* FDA presentation, FDA Evaluation Process of Foam Sclerosants, November, 2005.

K. BTG press release, Positive Interim Report of Varisolve® Phase II Safety Study to be Presented at SIR 2008 Scientific Meeting, March 17, 2008.

L. *Eckmann et al.,* Microvascular Embolization Following Polidocanol Microfoam Sclerosant Administration, *Dermatol. Surg.* (2005) 31:636-643.